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Reduced insulin sensitivity as a marker for acute mountain sickness?

Spliethoff, Kerstin ; Meier, Daniela ; Aeberli, Isabelle ; Gassmann, Max ; Langhans, Wolfgang ;
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Abstract: Spliethoff, Kerstin, Daniela Meier, Isabelle Aeberli, Max Gassmann, Wolfgang Langhans, Marco Maggiorini, Thomas A. Lutz, and Oliver Goetze. Reduced insulin sensitivity as a marker for acute mountain sickness? High Alt Med Biol 14:240–250, 2013—Reduced insulin sensitivity might increase the susceptibility to acute mountain sickness (AMS). The diabetogenic side effects of dexamethasone should therefore be considered for AMS treatment. To examine whether reduced insulin sensitivity is predictive of AMS and how it is affected by dexamethasone at high altitude, we analyzed endocrine and metabolic parameters obtained from healthy mountaineers in Zurich (LA; 490 m), and 2 and 4 days after fast ascent to the Capanna Regina Margherita (HA2, HA4; 4559 m). 14 of 25 participants developed AMS and were treated with dexamethasone starting in the evening of HA2. Before and after ingestion of an 1800 kJ meal, plasma was analyzed for erythropoietin (EPO) and cholecystokinin (CCK). Insulin sensitivity (HOMA-S) and beta cell activity were calculated. HOMA-S ($p < 0.01$) and EPO levels ($p < 0.05$) were lower in Zurich in the group developing AMS and given dexamethasone, i.e., before treatment and exposure to hypoxia. CCK was lower ($p < 0.01$) and glucose and insulin were higher on HA4 in the dexamethasone group compared to the untreated group. Individuals with low baseline insulin sensitivity and low baseline EPO levels were more susceptible to AMS. Reduced CCK may contribute to the beneficial effect of dexamethasone on high altitude anorexia. However, reduced insulin sensitivity questions the widespread use of dexamethasone to prevent/treat AMS.

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Reduced insulin sensitivity as a marker for acute mountain sickness?

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Running head: Insulin sensitivity and AMS

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Abstract

Reduced insulin sensitivity in a pre-diabetic state might increase the susceptibility to acute mountain sickness (AMS). Dexamethasone's diabetogenic side effects could therefore play a role in the medical treatment of AMS.

To examine whether reduced insulin sensitivity is predictive of AMS and how this parameter is affected by dexamethasone at high altitude, we analyzed endocrine and metabolic parameters obtained from healthy mountaineers who spent 5 days at an altitude of 4559m.

Blood samples were taken in Zurich (ZH;490m) and 2 and 4 days after a fast ascent to the Capanna Regina Margherita (MG2, MG4;4559m). 14 of 25 participants (15/10 m/f) developed AMS and were treated with dexamethasone starting in the evening of Day 2 until descent. Before and after ingestion of an 1800kJ solid meal, plasma was analyzed for several hormones including erythropoietin (EPO) and cholecystokinin (CCK). Insulin sensitivity (HOMA-S) and beta cell activity were calculated from measured fasting insulin and glucose blood levels.

HOMA-S ($p<0.01$) and EPO levels ($p<0.05$) were lower at baseline in Zurich in the dexamethasone group i.e. before any treatment and exposure to hypoxia. CCK was lower ($p<0.01$) and glucose and insulin were higher on MG4 in the dexamethasone group compared to the untreated group.

The main finding in our study was that individuals with low baseline insulin sensitivity and low baseline EPO levels were more susceptible to AMS. Reduced CCK secretion may contribute to the beneficial effect of dexamethasone on high altitude anorexia. However, reduced insulin sensitivity may question dexamethasone's widespread use to prevent/treat AMS.

Key words: High altitude, insulin resistance, dexamethasone, erythropoietin

Introduction

More and more people living at or near sea level spend their spare time with activities such as hiking, skiing or climbing at higher altitude (> 2500m above sea level). The numbers of patients with metabolic syndrome, decreased insulin sensitivity or manifest diabetes increase worldwide and antidiabetic treatments have improved in recent years. As a result more patients with metabolic problems expose themselves to hypoxic conditions and may therefore want to benefit from prophylactic treatments, including dexamethasone. Dexamethasone is often used by mountaineers to prevent or treat acute mountain sickness (AMS) (14, 21, 27).

AMS has an incidence of 15-80% depending on individual susceptibility, acclimatization, speed of ascent and maximum height reached above 2500m (13, 20, 32, 33). Most common symptoms of AMS are headache, insomnia, fatigue, dizziness, breathlessness, anorexia and nausea (13, 19, 46, 53).

The underlying molecular mechanisms for dexamethasone-mediated improvement of mountaineers suffering from AMS are complex and only partly understood. This is due to the fact that the primary cause of AMS is still not well known. Because hypoxia-induced systemic inflammation may play a role in the development of AMS (15, 22, 23), the anti-inflammatory and immunosuppressant action of dexamethasone could at least partly be responsible for dexamethasone's beneficial effects in AMS. Further, dexamethasone may modulate the release and action of gastrointestinal hormones that control food intake. Cholecystokinin (CCK), that has been shown to be increased in plasma at high altitude, may play a role in the development of AMS-caused anorexia (4). CCK is also known to be decreased by dexamethasone in cell cultures and in rats in-vivo (41).

Dexamethasone, however, has a wide range of undesired side effects. In addition to its immunosuppressant impact that potentially increases the risk of infections and impaired wound healing, glucocorticoids have catabolic and diabetogenic effects on fat and carbohydrate metabolism (25, 48, 50). Unfortunately for diabetics the risk of side effects of dexamethasone treatment is even higher than for healthy subjects because high altitude hypoxia itself may lead to changes in glucose homeostasis (17,

24). This may result in changed insulin requirements and, eventually, in a deterioration of their metabolic disorders.

Therefore, as a primary endpoint we investigated potential metabolic differences in patients with AMS in particular concerning insulin sensitivity, metabolites, glucose metabolism and gastrointestinal hormones. All these data were analyzed retrospectively depending on whether individuals required dexamethasone or not. Second, we also attempted to estimate the effect of the dexamethasone treatment in a subgroup of participants.

Methods

Subjects

Twenty-five healthy and experienced mountaineers (15 male; 22-60 years) were recruited by adverts in mountain journals. As we were interested in AMS and therefore avoided acclimatization, volunteers were not allowed to stay more than 3 nights above 2500m one month prior to the fast ascent. Exclusion criteria were chronic diseases, regular medication, history of transplantation, clinically significant heart valve diseases and congenital heart or lung disease. Most volunteers had a body mass index (BMI) between 18 and 25 kg/m², but two persons with a BMI slightly above 25 and one with a BMI of 31 were also included. Participants had to show normal eating behavior and were not allowed to require special diets. Eight subjects were known to have experienced high altitude pulmonary edema (HAPE) in past ascents to altitude. The Ethics Committee of the Canton of Zurich approved the study (EK-1677) that conformed to the declaration of Helsinki.

Study procedure and power calculation

We performed a power calculation to assess the sample size for the endpoint detection of a significant effect of dexamethasone on postprandial glucose concentrations. These calculations were based on a recent study by Abdelmannan et al. (1). Those authors tested different doses of dexamethasone on postprandial glucose concentrations in healthy volunteers after a 75g oral glucose tolerance test (OGTT) and measured an increase of blood glucose concentrations from 127 ± 7.1 mg/dL to 176 ± 19 mg/dL after a single dose of 8mg dexamethasone given 24h before the following OGTT. The carbohydrate amount given in the present study and the single dose treatment with dexamethasone were comparable to the experimental

settings in the previous study (carbohydrate content of the muffin 52.91 g). Based on these data we calculated a sample size of only 4 volunteers and decided that a sample of 25 healthy volunteers would be high enough to detect a significant difference for our endpoint (effect size $d_z = 2.9467321$, α error probability = 0.05, power ($1-\beta$ error probability) = 0.95 ; noncentrality parameter $\delta = 5.8934642$, critical $t = 3.1824463$, $df = 3$, analysis done by G*Power Version 3.1.3).

Subjects underwent baseline physical examinations to ensure they met the inclusion criteria. First blood samplings were done in Zurich (ZH, 490 m above sea level, pO_2 140-150 mmHg) to generate baseline values. Groups of 4-5 subjects each were then exposed to hypoxia using a fixed schedule; all experiments were performed in the summer of 2009 over a period of 5 weeks. Each group started at Day 0 in Alagna Valsesia (Italy, 1205 m), was transported by cable car to 3000 m, then walked to the Capanna Gnifetti at 3600 m (pO_2 94-103 mmHg) in the Monte Rosa region and stayed there overnight. On Day 1 the groups ascended to arrive in the late morning at the Capanna Regina Margherita (4559 m, pO_2 81-91 mmHg), where all tests at high altitude were done (Fig. 1).

AMS assessment and medication

Occurrence of AMS was assessed using the Lake Louise Score (LLS>5) and through medical examination by experienced physicians. This study was not designed to assess the effects of dexamethasone on high altitude physiology in a randomized double blind placebo controlled fashion. Therefore for safety reasons only subjects with high HAPE susceptibility, a LLS greater 5 in the morning or evening of MG2 or necessity identified by medical examination were treated with 2 x 8 mg/day dexamethasone (9-fluor-16a-methylprednisolone, Dexamethasone Galepharm, 4 mg, Galepharm AG, 8700 Kuesnacht, Switzerland) starting on the evening of MG2, i.e., after the last blood sample had been taken on that day. One person had to be treated with dexamethasone already earlier on Day 2 so that this subject was excluded from the analysis. Due to the occurrence of AMS, 14 subjects had to be treated with dexamethasone (DEX) and 11 served as untreated controls (CON).

Study design and sample processing

Blood gas analysis was done in blood taken from the arteria radialis using an ABL 5 blood gas analyzer (Radiometer, Copenhagen). Blood samples were taken at ground

level in Zurich (ZH) and on Days 2 and 4 (MG2 and MG4) at the Capanna Regina Margherita. On the morning of each test day, a venous catheter was placed in the forearm to allow for blood sampling. Blood sampling was performed in the morning before an ad libitum breakfast at 7am (fasted hormone levels, Figs 2 and 3), just before and 30, 60, 90, 120, 180, 240 min after a test meal of two muffins at 01:00 pm (1.76 g dietary fiber, 12.52 g protein, 18.06 g fat, 52.91 g carbohydrates, 1800 kJ), and between an additional muffin preload and ad libitum dinner at 07:00 pm of each test day. For dinner, subjects were offered pasta, bolognese sauce, grated parmesan cheese and two sorts of biscuits. They were free to choose what and how much of the different foods they wanted to eat; all food consumed was weighed on a kitchen scale to the nearest gram, and energy intake was calculated. EDTA-plasma samples were kept frozen in liquid nitrogen or stored in -80°C for later analysis.

Plasma analysis

Inflammation markers

Cortisol was determined by electrochemiluminescence (Elecsys® Cortisol, Roche, Switzerland). Interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) were measured using the Milliplex® MAP Human Cytokine/Chemokine Assay (Millipore). Erythropoietin (EPO) was determined with the Human Erythropoietin Immunoassay (Quantikine, IVD, R&D Systems, Minneapolis, USA).

Gastrointestinal hormones

The Milliplex® MAP Kit Human Endocrine (Millipore, Billerica, MA, USA) was used for amylin. Cholecystokinin (CCK-8; active) was measured using Radioimmunoassay Kits (Eurodiagnostica, Burgdorf, Switzerland) by Prof. Christoph Beglinger, University Hospital Basel, Switzerland.

Glucose homeostasis

Glucose was measured by an enzymatic UV-Test with a Cobas Mira analyzer (Roche, Switzerland) and insulin by an ultra-sensitive Human Insulin RIA Kit (Millipore).

Calculations

Homeostasis model assessment (insulin sensitivity: $\text{HOMA S} = (\text{glucose} \times \text{insulin}) / 22.5$); beta cell activity: $\text{HOMA B} = (20 \times \text{insulin}) / (\text{glucose} - 3.5)$), fasting glucose to insulin ratio (G:I) and quantitative insulin sensitivity check index

(QUICKI=1/((LOG(insulin))+LOG(glucose))) were calculated by using the measured values of fasting insulin (mU/l) and fasting glucose (mmol/l) (18, 36).

Statistics

Statistical analysis was performed with Graphpad Software (San Diego California, USA). Power Analysis was done using G*Power Version 3.1.3. Some data were skewed and had different variances. To compare two groups on one test day significance was determined by Students t-test with Welch's correction. For comparison of different test days within groups the Wilcoxon matched-pairs signed rank test was used. Two-way ANOVA with Bonferroni post-hoc tests were used to compare hormone and metabolite levels over the course of the day. Area under the curve (AUC) was calculated for various time periods for hormones with the value of the plasma sample "before muffin" set as baseline. AUC therefore indicates the changes in plasma levels relative to individual baselines. Odds ratios with confidence interval and Fisher's exact test were calculated to define the risk to develop AMS in subjects with baseline EPO plasma levels $I < 6$ mU/ml and a HOMA S level ≥ 2 at baseline in ZH. In the case of HOMA S one value equaled zero; 0.5 was therefore added to all values to make the calculation of the odds ratio possible. Significance was assumed with a p-value ≤ 0.05 .

Results

Baseline characteristics

No significant differences were found between the dexamethasone-treated (DEX) and untreated groups (CON) in BMI, body weight, age, gender and in systolic, diastolic blood pressure and peripheral oxygen saturation on any test day (Table 1). Eight out of the 25 subjects were known to have suffered from HAPE before.

Hypoxia and clinical high altitude illness

Both groups decreased their arterial PO_2 on MG2 and MG4 (mean of 12.4 ± 1.2 kPa in ZH to 5.2 ± 0.6 kPa on MG2 and 5.9 ± 0.6 on MG4; $p < 0.001$); mean peripheral oxygen saturation also decreased compared to baseline levels ($97.3 \pm 1.4\%$ in ZH to $75.3 \pm 8.5\%$ at MG2 and $81.5 \pm 7.3\%$ at MG4; $p < 0.001$).

Lake Louise Score (LLS) was increased in both groups on MG2 compared to ZH ($p < 0.01$) and tended to be higher in MG2DEX compared to MG2CON ($p = 0.07$). On

MG4 LLS decreased but the effect was only significant in the dexamethasone-treated group ($p < 0.05$ for MG2DEX vs. MG4DEX; $p = 0.16$ for MG2CON vs. MG4CON). In both groups LLS remained higher on MG4 compared to ZH ($p < 0.05$) (Fig. 2A).

As expected, plasma EPO levels were increased in all subjects on MG2; EPO then decreased from MG2 to MG4, but remained higher on MG4 compared to ZH (MG2CON and MG4CON to ZHCON $p < 0.01$; MG2DEX and MG4DEX to ZHDEX $p < 0.001$). EPO levels decreased from MG2 to MG4 in both groups, but were lower in MG4DEX than in MG4CON ($p < 0.05$) (Table 1). Unexpectedly, EPO levels were lower in the dexamethasone-treated group than in the untreated control group at baseline in ZH ($p < 0.05$) i.e. before any dexamethasone treatment (Table 1). The odds ratio for the risk of suffering from AMS for subjects with EPO levels < 6 mU/ml at baseline in ZH was 10.5 with a confidence interval (CI) of 1.36 - 81.09 and a p-value of 0.03 in the Fisher's exact test.

Blood Metabolites and insulin

Plasma glucose concentration was higher in MG4DEX than in MG4CON at most time points of the day ($p < 0.001$ morning, before muffin, 60, 90 min after muffin; $p < 0.01$ 30 min; $p < 0.05$ 120, 180, 240 min) (Fig. 3A). Other metabolites including betahydroxybutyrate, triglycerides, free fatty acids and lactate did not differ significantly across groups (data not shown).

Retrospective analysis of baseline data in ZH indicated that plasma insulin was higher in DEX compared to CON at 60 min ($p < 0.01$). Comparison of the study days within groups showed no significant difference at any time point in CON, but insulin was higher in DEX on MG2 compared to ZH 30 and 60 min postprandially (pp) (Fig. 3B, $p_{30} < 0.001$, $p_{60} < 0.01$). Two-way ANOVA revealed an overall effect of dexamethasone and altitude in MG4DEX compared to ZHDEX ($p < 0.001$), but did not detect a significant difference between time points. MG4DEX had higher levels at 30 and 60 min than MG2DEX ($p < 0.001$). Insulin levels were higher in MG4DEX than in MG4CON after the test meal and just before dinner ($p < 0.001$ 60, 90 min pp; $p < 0.01$ 30, 120 min pp; $p < 0.05$, 180 min pp, before ad lib) (Fig. 3B). Fig. 4A represents fasting insulin levels taken before breakfast and demonstrates higher levels in ZHDEX compared to ZHCON ($p < 0.01$) and in MG4DEX compared to MG4CON ($p < 0.001$).

The AUC of insulin was smaller in MG2DEX than in ZHDEX at the time points 30, 60 and 90 min ($p_{30} < 0.05$, $p_{60} < 0.01$, $p_{90} < 0.05$), and greater in MG4DEX than in ZHDEX at the time points 120, 180 and 240 min ($p_{120} < 0.05$, $p_{180} < 0.01$, $p_{240} < 0.001$). At 180 min MG4CON was greater than ZHCON ($p < 0.05$). At the time points 180 and 240 min the AUC of insulin was greater in MG4DEX than in MG4CON ($p < 0.05$)(data not shown).

Assessment of insulin sensitivity

Calculation of homeostasis model assessment (HOMA) levels indicated that insulin sensitivity (HOMA S) was lower in MG4DEX than in MG4CON ($p < 0.001$). While this effect was expected considering the known effect of dexamethasone on glucose metabolism, it is remarkable that insulin sensitivity also was lower in ZHDEX compared to ZHCON ($p < 0.01$) i.e. already at baseline before any treatment. The odds ratio for the risk of developing AMS for subjects with HOMA S baseline levels in $ZH \geq 2$ was calculated as 22.5 with a confidence interval of 1.1 - 480.3 and $p = 0.014$ in the Fisher's exact test. HOMA S increased in MG2CON compared to ZH ($p < 0.05$) and in MG4DEX compared to ZH ($p < 0.01$) (Fig. 4B). Beta cell activity (HOMA B) remained unchanged. Fasting glucose to insulin ratio (Fig. 4C) was lower in ZHDEX and MG2CON compared to ZHCON ($p < 0.05$, $p < 0.01$) and also lower in MG4DEX than in MG4CON ($p < 0.05$). QUICKI values were significantly lower in ZHDEX and MG2CON than in ZHCON ($p < 0.05$) and lower in MG4DEX compared to ZHDEX and MG4CON ($p < 0.01$, $p < 0.001$) (Fig. 4D).

Inflammation markers and cortisol

Endogenous cortisol was measured as an internal treatment control standard in all individuals before and after medication with dexamethasone (Fig. 2B). As expected, endogenous cortisol was markedly lower after treatment (MG4DEX vs. MG4CON $p < 0.001$). Retrospective analysis indicated, however, that endogenous cortisol did not differ between groups in ZH or at MG2; in other words, endogenous cortisol was only suppressed in dexamethasone-treated participants. Based on similar cortisol levels on MG2 and ZH in both groups, the ascent on Days 0 and 1 had no influence on MG2.

Plasma IL-6 concentrations increased in both groups on MG2 compared to ZH (CON $p < 0.05$, DEX $p < 0.01$). IL-6 tended to be lower on MG4 than on MG2, but this

difference was only significant in the control group ($p < 0.05$) and not in the dexamethasone-treated group (MG2DEX vs. MG4DEX, $p = 0.07$) (Fig. 2C).

Plasma TNF- α levels were lower in MG4DEX than in MG4CON ($p < 0.05$) (Fig. 2D).

CCK, Amylin

Plasma levels of amylin did not differ at individual time points across groups, i.e. there was no effect of either hypoxia or dexamethasone treatment. Amylin and CCK increased as expected after the muffin test meal in both groups and on all days. (Fig 3 C)

Interestingly, CCK levels were lower in MG4DEX compared to MG4CON 30 min ($p < 0.05$) and 60 min ($p < 0.01$) after the test meal (Fig. 3C). The AUC of CCK was also smaller in DEX compared to CON on MG2 30, 60 and 90 min after the test meal ($p < 0.05$). The AUC was greater in MG4CON compared to ZH 30, 60 and 90 min postprandially ($p_{30} < 0.01$, $p_{60} < 0.01$, $p_{90} < 0.05$); compared to MG4DEX, it remained higher over all time points after the muffin test meal (before breakfast $p < 0.05$, all other time points $p < 0.01$) (data not shown).

Amylin had a greater AUC at MG2 in CON 30 and 60 min after the muffin test meal ($p < 0.05$). Ninety to 240 min after the muffin the AUC of amylin was greater in CON at MG2 than on ZH ($p < 0.001$) (data not shown).

Similarly, we also measured PYY and gastrin over the course of the study but did not detect any differences among groups (data not shown).

Caloric intake ad libitum dinner

Energy intake (kcal) during the ad libitum dinner was lower in DEX on all three days ($p < 0.05$) and was decreased in both groups on MG2 compared to ZH (ZHCON vs. MG2CON $p < 0.01$; ZHDEX vs. MG2DEX $p < 0.05$). Energy intake returned to nearly baseline levels on MG4 (MG2CON vs. MG4CON $p < 0.05$; MG2DEX vs. MG4DEX $p < 0.01$) (Fig. 5).

Taken together, our findings indicate that baseline insulin sensitivity and baseline EPO levels were lower in individuals at risk of AMS; these individuals required dexamethasone treatment in the evening of MG2 because of the development of AMS.

Discussion

The exact causes and mechanisms of AMS remain unknown. Here we intended primarily to study specifically the effects of AMS on pre- and postprandial metabolism of a caloric solid meal. Second we were interested in side effects of dexamethasone treatment on metabolism in AMS prone patients when exposed to high altitude-induced hypoxia. Our results did not only confirm the expected effect of dexamethasone on glucose homeostasis but also revealed differences between the two groups in plasma EPO levels and insulin sensitivity already at baseline in Zurich, i.e., at low altitude and before treatment with dexamethasone.

The clinical appearance of AMS, as reflected by the Lake Louise Score (LLS), was induced by the fast ascent to high altitude with an increase on MG2 and a decrease due to acclimatization on MG4 in both groups as expected (20, 26). The prevalence of 57% of AMS in our subjects lies within the upper range of the data reported by other groups that found a prevalence of 30-60% at altitudes between 4243m and 5671m (5, 20, 32, 54). This may be due to the fast ascent in our study and to the study design that included eight subjects with known HAPE susceptibility. The decrease in LLS on MG4 after dexamethasone clearly shows the effective improvement in well-being of the subjects who suffered from AMS but were successfully treated with dexamethasone, as it has been reported previously (49).

Endogenous cortisol was measured and analyzed to proof dexamethasone's efficacy. The suppressive effect of dexamethasone on endogenous cortisol production was as expected (9, 38), i.e., the dexamethasone-treated group showed a marked decrease in the plasma levels of endogenous cortisol at MG4. Hence, the medication of the individuals suffering from AMS was considered successful.

Cytokines

Consistent with other studies, the plasma concentration of IL-6 - but not of the other cytokines - increased due to exposure to high altitude hypoxia. (15, 23). Plasma IL-6 and TNF- α decreased in the dexamethasone-treated group on MG4, an expected observation due to the anti-inflammatory effect of dexamethasone.

EPO

Erythropoietin expression is up-regulated by hypoxia (8). As expected, plasma EPO levels therefore increased on MG2 after the fast ascent. Endogenous EPO has a relatively short plasma half-life of 6-9 hours (8). Our results therefore indicate that the

EPO production was still higher on MG4 compared to ZH but lower compared to MG2. The significantly lower EPO plasma level in the dexamethasone-treated group on MG4 can be explained by the effect of dexamethasone on gene transcription of cytokines via the glucocorticoid receptor (3, 39, 47). Hypoxia inducible factor (HIF) enhances EPO gene transcription in response to hypoxia (51), and Gaber et al. showed in cultured cells that dexamethasone suppresses the expression of HIF (12). Unfortunately this effect interferes with the acclimatization to high altitude hypoxia and, hence, contributes to the necessity to descend in case of AMS despite medication with dexamethasone. Further possible influences on plasma EPO levels such as EPO clearance from blood, have not well been investigated yet.

In apparent contrast to our study Pavlicek et al. reported no difference in baseline levels but a significantly higher EPO plasma level in HAPE susceptible subjects at high altitude (40). Of note, one of the inclusion criteria for our study was, that the subjects were not allowed to spend more than 3 nights at 2500 m or higher one month prior to the study, but we did not completely exclude activities at altitude. Altitude activities prior to the study and a better general state of physical fitness may have lead to the slightly but significantly higher EPO levels in ZH in the group that did not suffer from AMS (11). However, another study (45), which also included some of the subjects who participated in our experiments, found that VO_{2max} as parameter for aerobic capacity did not differ between HAPE susceptible and control subjects. Hence, our results do not clearly indicate, whether there is a direct connection between plasma EPO levels at near sea level and susceptibility to AMS.

Glucose metabolism

Glucose metabolism was affected by dexamethasone on MG4 as expected. Dexamethasone has been shown to increase glucose levels in other studies [e.g. (35)]. We could not confirm, however, the increased glucose levels due to hypoxia or AMS itself reported by Larsen et al. (24). Glucocorticoids affect glucose metabolism in several ways, they impair insulin dependent glucose uptake in the periphery and enhance gluconeogenesis in the liver (42, 43).

Our data show that glucose and insulin levels increased and, hence, insulin sensitivity decreased after dexamethasone treatment on MG4, which was expected (1). No significant changes due to hypoxia could be seen on MG2. Surprisingly, however, we found a lower insulin sensitivity in Zurich at baseline – which has to be

clearly differentiated from diagnosed diabetes – in the subjects that later suffered from AMS and had to be treated with dexamethasone. This may be an indication of higher susceptibility of those individuals for AMS. We did not evaluate the subjects with respect to any hereditary predisposition for diabetes. Of note Henriksen et al showed that dexamethasone differentially alters muscle glucose metabolism of normoglycemic relatives of type 2 diabetic patients (17). The lower plasma EPO levels in the dexamethasone-treated group already at baseline may also contribute to reduced insulin sensitivity because it has been shown that EPO improves glucose tolerance in mice by changing muscle metabolism (10, 22, 32), and because EPO treatment of anemia in uremic patients improved insulin resistance and alleviated hyperinsulinemia (34).

Insulin sensitivity is impaired in patients with metabolic syndrome, but other symptoms such as increased blood pressure or higher BMI did not appear to be prevalent in our subjects (44). Although they did not yet show any obvious symptoms of diabetes or even overt changes in blood glucose levels, people predisposed for diabetes may have more difficulties to handle those side effects of dexamethasone because they aggravate their insulin resistance, that might have been undetected before. Therefore we analyzed insulin sensitivity by different models using fasting insulin and glucose levels, but all yielded consistent findings. We did not perform hyperinsulinemic-euglycemic clamps or oral glucose tolerance tests in our study. Another possible indicator for assessing the blood glucose concentration over a longer period of time is glycated hemoglobin (HbA1c) (6, 16). Nevertheless, we are convinced that the calculations of HOMA, QUICKI, glucose to insulin ratio combined with the values of fasting insulin are helpful and reliable indices to assess insulin resistance (18, 36, 37).

Hormones

Plasma CCK levels of MG4CON tended to be higher at one time point (30 min postprandially) compared to ZH and MG2, but this difference did not reach statistical significance. We could therefore not confirm the increase in resting plasma CCK that Bailey et al. found at high altitude (4). The AUC revealed a significantly higher increase of CCK in MG4CON compared to ZH and MG4DEX, which may indicate that hypoxia could still have had some influence. This finding, combined with the significantly lower levels in MG4DEX compared to MG4CON, confirms an effect of

dexamethasone on CCK levels similar to what had already been reported by Gatineau et al. in both, cell culture and rat experiments (41). Therefore, the decrease in CCK may play a role in the improvement of AMS-associated anorexia after dexamethasone treatment.

Although we found no significant difference at single time points in amylin plasma levels that would implicate an effect of hypoxia or dexamethasone, we observed significant differences in the postprandial AUC. The AUC revealed that amylin increased more in MG2CON compared to MG2DEX at the time points 30 and 60 min and compared to ZHCON for the time points 90, 120, 180 and 240 min. Therefore the food intake induced amylin response seems to be different in subjects at high altitude compared to sea level and compared to subjects suffering from AMS. This needs to be further investigated but at least our data suggest that dexamethasone has no effect on amylin plasma levels.

Caloric intake

The overall effect of hypoxia on eating, in particular the significant decrease of caloric intake during the ad libitum dinner in both groups on MG2 confirms the results of earlier studies (28, 52). The increase in caloric intake back to nearly baseline (ZH) levels in both groups on MG4 was probably due to acclimatization and the dexamethasone treatment in the DEX group (7). Subjects at risk for AMS (DEX) ate less than the control group on all three test days. As we did not measure hormone levels and metabolites during and after the ad libitum dinner, potential mechanisms need to be tested in future studies. For detailed analysis of caloric intake in our test subjects please see Aeberli et al. (2).

Finally, some limitations of our study need to be mentioned. First, medication was not blinded and we had no placebo control group included due to the primary endpoint of this large-scale study. In other words, any individual who required dexamethasone treatment due to medical condition and development of AMS received the drug. The other individuals remained untreated. Nonetheless, we believe that the main conclusion of our study, i.e., that low insulin sensitivity may predispose for AMS when exposed to hypoxia, is interesting and remains valid. As the data were analyzed retrospectively, we did not carry out oral glucose tolerance tests or hyperinsulinemic-euglycemic clamps that would have allowed for stronger conclusions concerning the state of glucose metabolism. Second, due to some technical difficulties in blood

sampling under field conditions and analysis, the group size (n) for some parameters is rather small.

To summarize, our results provide evidence indicating that dexamethasone in the treatment of AMS has not only positive effects on inflammation and altitude anorexia, but also carries the risk of a potentially dangerous influence on glucose metabolism, in particular as our data indicate that people with decreased insulin sensitivity may be more susceptible to AMS. Finally, this study emphasizes a clear need for further investigation and reminds the reader that dexamethasone is a potent drug but, due to the numerous possible side effects, also potentially dangerous, when taken at high altitude.

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None of the authors has any conflict of interest with regard to this manuscript.

1. **Abdelmannan D, Tahboub R, Genuth S, and Ismail-Beigi F.** Effect of dexamethasone on oral glucose tolerance in healthy adults. *Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists* 16: 770-777, 2010.
2. **Aeberli I, Erb A, Spliethoff K, Meier D, Gotze O, Fruhauf H, Fox M, Finlayson GS, Gassmann M, Berneis K, Maggiorini M, Langhans W, and Lutz TA.** Disturbed eating at high altitude: influence of food preferences, acute mountain sickness and satiation hormones. *Eur J Nutr*, 2012.
3. **Amano Y, Lee SW, and Allison AC.** Inhibition by glucocorticoids of the formation of interleukin-1 alpha, interleukin-1 beta, and interleukin-6: mediation by decreased mRNA stability. *Mol Pharmacol* 43: 176-182, 1993.
4. **Bailey DM, Davies B, Milledge JS, Richards M, Williams SR, Jordinson M, and Calam J.** Elevated plasma cholecystokinin at high altitude: metabolic implications for the anorexia of acute mountain sickness. *High altitude medicine & biology* 1: 9-23, 2000.
5. **Basnyat B, Lemaster J, and Litch JA.** Everest or bust: a cross sectional, epidemiological study of acute mountain sickness at 4243 meters in the Himalayas. *Aviat Space Environ Med* 70: 867-873, 1999.
6. **Borges JL, Bilezikian JP, Jones-Leone AR, Acosta AP, Ambery PD, Nino AJ, Grosse M, Fitzpatrick LA, and Cobitz AR.** A Randomized, Parallel Group, Double-blind, Multicentre Study Comparing the Efficacy and Safety of Avandamet (Rosiglitazone/Metformin) and Metformin on Long-term Glycaemic Control and Bone Mineral Density after 80 Weeks of Treatment in Drug-naive Type 2 Diabetes Mellitus Patients. *Diabetes Obes Metab*, 2011.

7. **Bruera E, Moyano JR, Sala R, Rico MA, Bosnjak S, Bertolino M, Willey J, Strasser F, and Palmer JL.** Dexamethasone in addition to metoclopramide for chronic nausea in patients with advanced cancer: a randomized controlled trial. *J Pain Symptom Manage* 28: 381-388, 2004.
8. **Eckardt KU, Boutellier U, Kurtz A, Schopen M, Koller EA, and Bauer C.** Rate of erythropoietin formation in humans in response to acute hypobaric hypoxia. *J Appl Physiol* 66: 1785-1788, 1989.
9. **Findling JW, Raff H, and Aron DC.** The low-dose dexamethasone suppression test: a reevaluation in patients with Cushing's syndrome. *J Clin Endocrinol Metab* 89: 1222-1226, 2004.
10. **Foskett A, Alnaeeli M, Wang L, Teng R, and Noguchi CT.** The effects of erythropoietin dose titration during high-fat diet-induced obesity. *J Biomed Biotechnol* 2011: 373781, 2011.
11. **Frese F and Friedmann-Bette B.** Effects of repetitive training at low altitude on erythropoiesis in 400 and 800 m runners. *Int J Sports Med* 31: 382-388, 2010.
12. **Gaber T, Schellmann S, Erekul KB, Fangradt M, Tykwinska K, Hahne M, Maschmeyer P, Wagegg M, Stahn C, Kolar P, Dziurla R, Lohning M, Burmester GR, and Buttgereit F.** Macrophage migration inhibitory factor counterregulates dexamethasone-mediated suppression of hypoxia-inducible factor-1 alpha function and differentially influences human CD4+ T cell proliferation under hypoxia. *J Immunol* 186: 764-774, 2011.
13. **Hackett PH, Rennie D, and Levine HD.** The incidence, importance, and prophylaxis of acute mountain sickness. *Lancet* 2: 1149-1155, 1976.
14. **Hackett PH, Roach RC, Wood RA, Foutch RG, Meehan RT, Rennie D, and Mills WJ, Jr.** Dexamethasone for prevention and treatment of acute mountain sickness. *Aviat Space Environ Med* 59: 950-954, 1988.
15. **Hartmann G, Tschop M, Fischer R, Bidlingmaier C, Riepl R, Tschop K, Hautmann H, Endres S, and Toepfer M.** High altitude increases circulating interleukin-6, interleukin-1 receptor antagonist and C-reactive protein. *Cytokine* 12: 246-252, 2000.
16. **Heianza Y, Hara S, Arase Y, Saito K, Fujiwara K, Tsuji H, Kodama S, Hsieh SD, Mori Y, Shimano H, Yamada N, Kosaka K, and Sone H.** HbA1c 5.7-6.4% and impaired fasting plasma glucose for diagnosis of prediabetes and risk of progression to diabetes in Japan (TOPICS 3): a longitudinal cohort study. *Lancet* 378: 147-155, 2011.
17. **Henriksen JE, Alford F, Vaag A, Handberg A, and Beck-Nielsen H.** Intracellular skeletal muscle glucose metabolism is differentially altered by dexamethasone treatment of normoglycemic relatives of type 2 diabetic patients. *Metabolism: clinical and experimental* 48: 1128-1135, 1999.
18. **Hung AM, Sundell MB, Egbert P, Siew ED, Shintani A, Ellis CD, Bian A, and Ikizler TA.** A comparison of novel and commonly-used indices of insulin sensitivity in African American chronic hemodialysis patients. *Clin J Am Soc Nephrol* 6: 767-774, 2011.
19. **Imray C, Wright A, Subudhi A, and Roach R.** Acute mountain sickness: pathophysiology, prevention, and treatment. *Progress in cardiovascular diseases* 52: 467-484, 2010.
20. **Jackson SJ, Varley J, Sellers C, Josephs K, Codrington L, Duke G, Njelekela MA, Drummond G, Sutherland AI, Thompson AA, and Baillie JK.** Incidence and predictors of acute mountain sickness among trekkers on Mount Kilimanjaro. *High altitude medicine & biology* 11: 217-222, 2010.

21. **Johnson TS, Rock PB, Fulco CS, Trad LA, Spark RF, and Maher JT.** Prevention of acute mountain sickness by dexamethasone. *N Engl J Med* 310: 683-686, 1984.
22. **Julian CG, Subudhi AW, Wilson MJ, Dimmen AC, Pecha T, and Roach RC.** Acute Mountain Sickness, Inflammation and Permeability: New Insights from a Blood Biomarker Study. *J Appl Physiol*, 2011.
23. **Klausen T, Olsen NV, Poulsen TD, Richalet JP, and Pedersen BK.** Hypoxemia increases serum interleukin-6 in humans. *European journal of applied physiology and occupational physiology* 76: 480-482, 1997.
24. **Larsen JJ, Hansen JM, Olsen NV, Galbo H, and Dela F.** The effect of altitude hypoxia on glucose homeostasis in men. *J Physiol* 504 (Pt 1): 241-249, 1997.
25. **Lee MJ, Gong DW, Burkey BF, and Fried SK.** Pathways regulated by glucocorticoids in omental and subcutaneous human adipose tissues: a microarray study. *American journal of physiology* 300: E571-580, 2011.
26. **Leshem E, Pandey P, Shlim DR, Hiramatsu K, Sidi Y, and Schwartz E.** Clinical features of patients with severe altitude illness in Nepal. *Journal of travel medicine* 15: 315-322, 2008.
27. **Levine BD, Yoshimura K, Kobayashi T, Fukushima M, Shibamoto T, and Ueda G.** Dexamethasone in the treatment of acute mountain sickness. *N Engl J Med* 321: 1707-1713, 1989.
28. **Lippl FJ, Neubauer S, Schipfer S, Lichter N, Tufman A, Otto B, and Fischer R.** Hypobaric hypoxia causes body weight reduction in obese subjects. *Obesity (Silver Spring)* 18: 675-681, 2010.
29. **Luks AM, McIntosh SE, Grissom CK, Auerbach PS, Rodway GW, Schoene RB, Zafren K, and Hackett PH.** Wilderness Medical Society consensus guidelines for the prevention and treatment of acute altitude illness. *Wilderness Environ Med* 21: 146-155, 2010.
30. **Luks AM and Swenson ER.** Medication and dosage considerations in the prophylaxis and treatment of high-altitude illness. *Chest* 133: 744-755, 2008.
31. **Maggiorini M.** Prevention and treatment of high-altitude pulmonary edema. *Progress in cardiovascular diseases* 52: 500-506, 2010.
32. **Maggiorini M, Buhler B, Walter M, and Oelz O.** Prevalence of acute mountain sickness in the Swiss Alps. *Bmj* 301: 853-855, 1990.
33. **Mairer K, Wille M, and Burtcher M.** The prevalence of and risk factors for acute mountain sickness in the Eastern and Western Alps. *High altitude medicine & biology* 11: 343-348, 2010.
34. **Mak RH.** Correction of anemia by erythropoietin reverses insulin resistance and hyperinsulinemia in uremia. *The American journal of physiology* 270: F839-844, 1996.
35. **Marquet P, Lac G, Chassain AP, Habrioux G, and Galen FX.** Dexamethasone in resting and exercising men. I. Effects on bioenergetics, minerals, and related hormones. *J Appl Physiol* 87: 175-182, 1999.
36. **Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, and Turner RC.** Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28: 412-419, 1985.
37. **McAuley KA, Williams SM, Mann JI, Walker RJ, Lewis-Barned NJ, Temple LA, and Duncan AW.** Diagnosing insulin resistance in the general population. *Diabetes Care* 24: 460-464, 2001.

38. **Miller AH, Spencer RL, Pulera M, Kang S, McEwen BS, and Stein M.** Adrenal steroid receptor activation in rat brain and pituitary following dexamethasone: implications for the dexamethasone suppression test. *Biol Psychiatry* 32: 850-869, 1992.
39. **Newton R, King EM, Gong W, Rider CF, Staples KJ, Holden NS, and Bergmann MW.** Glucocorticoids inhibit IL-1 β -induced GM-CSF expression at multiple levels: roles for the ERK pathway and repression by MKP-1. *Biochem J* 427: 113-124, 2010.
40. **Pavlicek V, Marti HH, Grad S, Gibbs JS, Kol C, Wenger RH, Gassmann M, Kohl J, Maly FE, Oelz O, Koller EA, and Schirilo C.** Effects of hypobaric hypoxia on vascular endothelial growth factor and the acute phase response in subjects who are susceptible to high-altitude pulmonary oedema. *Eur J Appl Physiol* 81: 497-503, 2000.
41. **Ratineau C, Roche C, Chuzel F, Cordier-Bussai M, Blanc M, Bernard C, Cuber JC, and Chayvialle JA.** Regulation of intestinal cholecystokinin gene expression by glucocorticoids. *J Endocrinol* 151: 137-145, 1996.
42. **Rizza RA, Mandarino LJ, and Gerich JE.** Cortisol-induced insulin resistance in man: impaired suppression of glucose production and stimulation of glucose utilization due to a postreceptor defect of insulin action. *J Clin Endocrinol Metab* 54: 131-138, 1982.
43. **Rooney DP, Neely RD, Cullen C, Ennis CN, Sheridan B, Atkinson AB, Trimble ER, and Bell PM.** The effect of cortisol on glucose/glucose-6-phosphate cycle activity and insulin action. *J Clin Endocrinol Metab* 77: 1180-1183, 1993.
44. **Salazar MR, Carbajal HA, Espeche WG, Dulbecco CA, Aizpurua M, Marillet AG, Echeverria RF, and Reaven GM.** Relationships among insulin resistance, obesity, diagnosis of the metabolic syndrome and cardio-metabolic risk. *Diab Vasc Dis Res* 8: 109-116, 2011.
45. **Siebenmann C, Bloch KE, Lundby C, Nussbamer-Ochsner Y, Schoeb M, and Maggiorini M.** Dexamethasone improves maximal exercise capacity of individuals susceptible to high altitude pulmonary edema at 4559 m. *High altitude medicine & biology* 12: 169-177, 2011.
46. **Silber E, Sonnenberg P, Collier DJ, Pollard AJ, Murdoch DR, and Goadsby PJ.** Clinical features of headache at altitude: a prospective study. *Neurology* 60: 1167-1171, 2003.
47. **Smith PJ, Cousins DJ, Jee YK, Staynov DZ, Lee TH, and Lavender P.** Suppression of granulocyte-macrophage colony-stimulating factor expression by glucocorticoids involves inhibition of enhancer function by the glucocorticoid receptor binding to composite NF-AT/activator protein-1 elements. *J Immunol* 167: 2502-2510, 2001.
48. **Sood A and Ismail-Beigi F.** Effect of dexamethasone on insulin secretion: examination of underlying mechanisms. *Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists* 16: 763-769, 2010.
49. **Subudhi AW, Dimmen AC, Julian CG, Wilson MJ, Panerai RB, and Roach RC.** Effects of acetazolamide and dexamethasone on cerebral hemodynamics in hypoxia. *J Appl Physiol* 110: 1219-1225, 2011.
50. **Wajngot A, Giacca A, Grill V, Vranic M, and Efendic S.** The diabetogenic effects of glucocorticoids are more pronounced in low- than in high-insulin responders. *Proceedings of the National Academy of Sciences of the United States of America* 89: 6035-6039, 1992.

51. **Wang GL and Semenza GL.** Purification and characterization of hypoxia-inducible factor 1. *J Biol Chem* 270: 1230-1237, 1995.
52. **Westerterp-Plantenga MS, Westerterp KR, Rubbens M, Verwegen CR, Richelet JP, and Gardette B.** Appetite at "high altitude" [Operation Everest III (Comex-'97)]: a simulated ascent of Mount Everest. *J Appl Physiol* 87: 391-399, 1999.
53. **Wu TY, Ding SQ, Zhang SL, Duan JQ, Li BY, Zhan ZY, Wu QL, Baomu S, Liang BZ, Han SR, Jie YL, Li G, Sun L, and Kayser B.** Altitude illness in Qinghai-Tibet railroad passengers. *High altitude medicine & biology* 11: 189-198, 2010.
54. **Ziaee V, Yunesian M, Ahmadinejad Z, Halabchi F, Kordi R, Alizadeh R, and Afsharjoo HR.** Acute mountain sickness in Iranian trekkers around Mount Damavand (5671 m) in Iran. *Wilderness Environ Med* 14: 214-219, 2003.

Fig. 1
Scheme of study travel itinerary

Fig. 2 Inflammation and clinical AMS

Effects of hypoxia and dexamethasone on Lake Louise score (LLS) (A; n CON=11, DEX=14) and on plasma concentrations of cortisol (B; n CON=9, DEX=12), interleukin-6 (IL-6) (C; n CON=9, DEX=11), tumor necrosis factor alpha (TNF α) (D; n CON=9, DEX=11).

§ indicates significant differences within the groups between different test days, tested with Wilcoxon matched-pairs signed rank test.

* indicates significant differences between the groups on the same test day, tested with unpaired Students t-test with Welch's correction

§, *: $p < 0.05$, §§, **: $p < 0.01$, §§§, ***: $p < 0.001$

Error bars represent standard error of the mean.

ZH: Zurich, baseline; MG2: Day 2 and MG4: Day 4 at the Capanna Regina Margherita;

Fig. 3 CCK and glucose metabolism, whole day

Plasma levels of glucose (A), insulin (B) and CCK (C) in Zurich (ZH) and on Day 2 (MG2) and Day 4 (MG4) at high altitude, measured nine times each day and separated retrospectively into two groups (dexamethasone-treated (DEX) and control group (CON)).

*Indicates significant differences between MG4CON and MG4DEX;

§ indicates significant differences between ZHCON and ZHDEX

§, *: $p < 0.05$, §§, **: $p < 0.01$, §§§, ***: $p < 0.001$

Error bars represent standard error of the mean.

ZH: Zurich, baseline; MG2: Day 2 and MG4: Day 4 at the Capanna Regina Margherita;

Fig. 4 Glucose metabolism, fasted state

Effects of hypoxia and dexamethasone on fasting insulin (A; n CON=9, DEX=12) in the first sample of each test day, insulin sensitivity by homeostasis model assessment (HOMA S) (B; n CON=9, DEX=12), fasting glucose to insulin ratio (G:I) (C; n CON=9, DEX=12) and quantitative insulin sensitivity check index (QUICKI) (D; n CON=9, DEX=12)

§ indicates significant differences within the groups between different test days, tested with Wilcoxon matched-pairs signed rank test.

* indicates significant differences between the groups on the same test day, tested with unpaired Students t-test with Welch's correction

§, *: $p < 0.05$, §§, **: $p < 0.01$, §§§, ***: $p < 0.001$

Error bars represent standard error of the mean.

ZH: Zurich, baseline; MG2: Day 2 and MG4: Day 4 at the Capanna Regina Margherita;

Fig. 5 Food intake at ad libitum dinner (CON=9, DEX=12)

§ indicates significant differences within the groups between different test days, tested with Wilcoxon matched-pairs signed rank test.

* indicates significant differences between the groups on the same test day, tested with unpaired Students t-test with Welch's correction

§, *: $p < 0.05$, §§, **: $p < 0.01$, §§§, ***: $p < 0.001$

Error bars represent standard error of the mean.

ZH: Zurich, baseline; MG2: Day 2 and MG4: Day 4 at the Capanna Regina Margherita;

4559m

Capanna Regina Margherita

3600m

Capanna
Gnifetti

490m

USZ

ZH

day 0

day 1

day 2

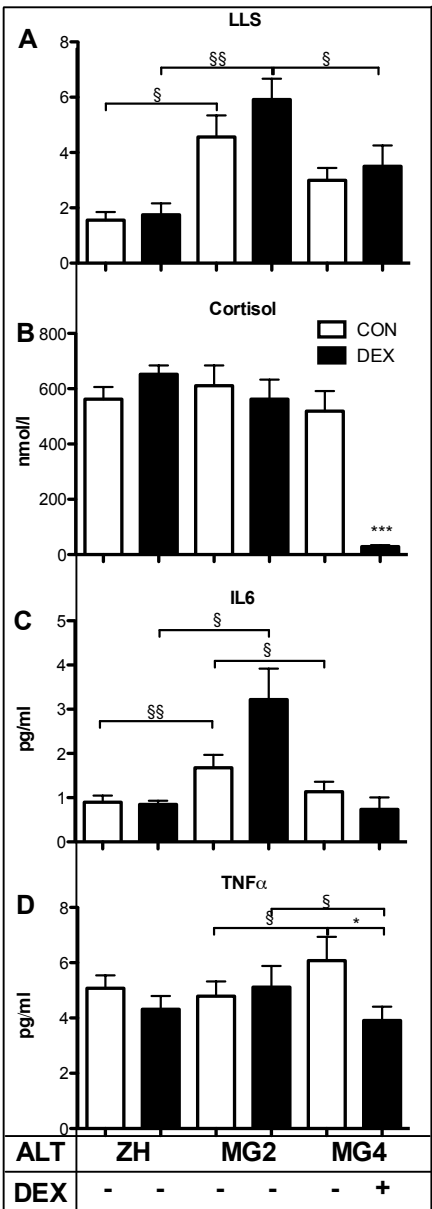
MG2

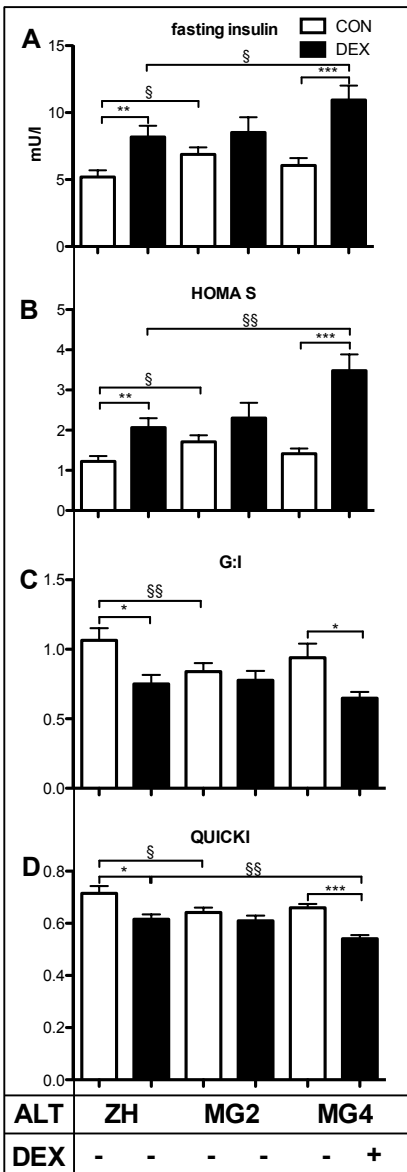
day 3

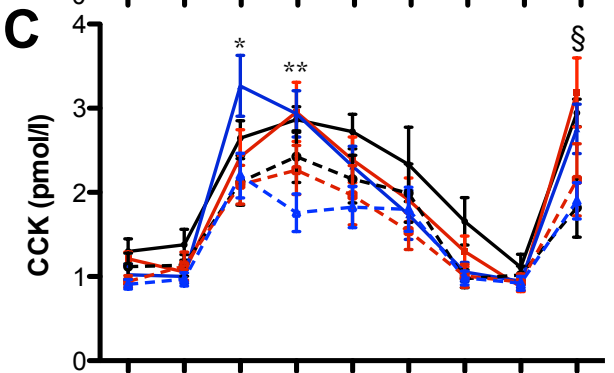
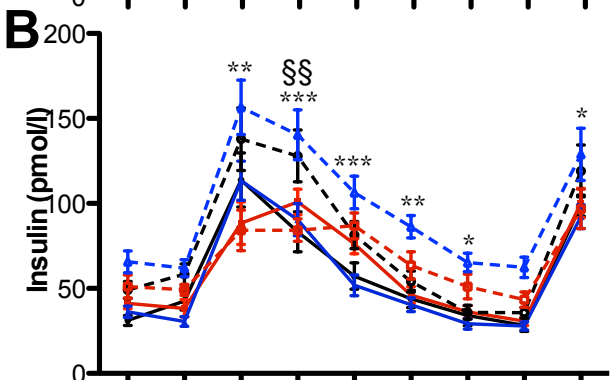
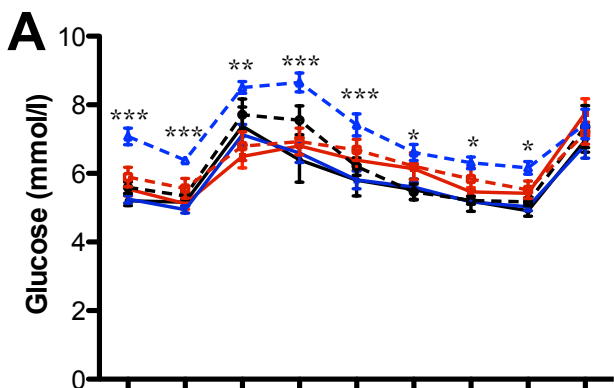
day 4

MG4

day 5







—●— ZHCON

—●— ZHDEX

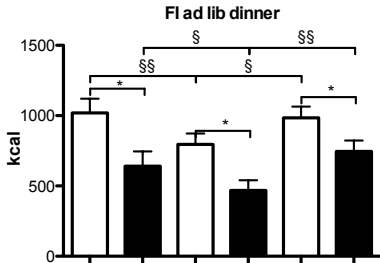
—■— MG2CON

—■— MG2DEX

—■— MG4CON

—■— MG4DEX

CON n=9; DEX n=12



ALT	ZH		MG2		MG4	
DEX	-	-	-	-	-	+

Table 1. baseline characteristics

	ZH		MG2		MG4	
	CON	DEX	CON	DEX	CON	DEX
age	39.8 ± 10.4	46.5 ± 8.8				
BW	72.0 ± 7.5	70.0 ± 12.1				
BMI	23.5 ± 1.1	23.9 ± 2.8				
SBP	127 ± 14	131 ± 14	132 ± 12	125 ± 12	137 ± 11	129 ± 13
DBP	76 ± 11	80 ± 8	81 ± 7	78 ± 9	83 ± 8	80 ± 5
EPO	7.2 ± 1.7	5.4 ± 2.0*	78.4 ± 33.8 ^{§§§}	69.0 ± 22.2 ^{§§§}	41.0 ± 17.3 ^{§§§}	23.3 ± 8.5 ^{**§§§}
SPO2	97.2 ± 1.6	97.3 ± 1.3	78.8 ± 6.6 ^{§§§}	72.5 ± 9.1 ^{§§§}	83.4 ± 6.2 ^{§§§}	79.9 ± 7.9 ^{§§§}

Subjects divided in dexamethasone treated group (DEX) and control group (CON); table includes age, body weight (BW; kg), body mass index (BMI; kg/m²), systolic (SBP; mmHg) and diastolic blood pressure (DBP; mmHg), erythropoietin (EPO; mU/ml), peripheral oxygen saturation (SPO2; kPa). ZH: Zurich, baseline; MG2: day 2 and MG4: day 4 at the Capanna Regina Margherita.

Values are means ± SD; * indicates a significant difference to control at the same day, § indicates a significant difference within the same group to baseline in ZH; §, *: p<0.05, §§, **: p<0.01, §§§, ***: p<0.001